REMARKS

I. Status of the Claims

Claims 69 and 70 are pending in the present application.

II. The Rejections

A. Rejection of Claims 69 and 70 under 35 U.S.C. §112, First Paragraph (Written Description)

On page 2 of the Office Action claims 69 and 70 remain rejected under 35 U.S.C. §112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the invention. Applicants respectfully traverse the rejection.

Dhanoa Declaration Has Not been Considered for the Relevant Issue

The basis for the rejection is that generally disclosing using the invention for drug discovery does not reasonably convey the specific steps in the claims. Page 5 of the Office Action, paragraph that spans pages 4-5. Applicants disagree. This specific issue has been addressed in an expert Declaration in this file history. Up to the present, however, this Declaration has not been considered *for its substance on this issue.*

The Declaration of Dr. Dale Dhanoa, a qualified expert in the field of drug discovery, was presented in Applicants' Response dated July 10, 2003. Based on detailed scientific evidence Dr. Dhanoa reached the following conclusion:

> Based on my reading of the patent application, therefore, it is my opinion that the person of ordinary skill in the field of drug discovery, reading this application on or about the filing date of September 26, 1997, would have realized that the Applicants, by mentioning the drug discovery process as they did, implicitly were describing the drug discovery method in claims 62-69, copy attached.

Dhanoa Declaration page 9. This Declaration was submitted specifically to address the issue of whether the steps in the claims were reasonably conveyed to the person of ordinary skill in the art. The steps currently at issue were in claims 62-69, which the Declaration considered. Therefore, the Declaration applies to the current claims as well. A copy of claims 62-69 is attached as Appendix A.

The Examiner dismisses this Declaration, asserting that it was submitted to address a *different issue*. The Examiner states:

> It is emphasized that the Declaration was previously submitted in response to a written description requirement rejection for *description of compounds* in the Office Action of 1/13/03 and that the rejection was withdrawn after the consideration of the Declaration (see the Advisory Action of 8/5/03).

Office Action, page 4. Italics added.

This statement is factually incorrect. Contrary to the Examiner's assertion, the Declaration was submitted to address the issue at hand.

The Dhanoa Declaration addressed the question of what the person of ordinary skill in the art would have understood from the statements in the specification about using the invention for drug discovery. The Dhanoa Declaration was not concerned with the adequacy of written description of the compounds. Therefore, the Examiner's statement is factually

incorrect and the Declaration has not been considered for its evidence on the pertinent issue. Because the Declaration has not been considered for the correct issue, the rejection is improperly supported.

Applicants have already clearly stated why they submitted the Dhanoa Declaration. In Applicants' Response dated July 10, 2003, Applicants spelled this out in detail. Briefly, during an interview held on May 16, 2003, Examiner Reynolds explained that, based on her review of the text directed to drug discovery in the specification, the specification did not describe the steps of compound testing on the cells to which the invention is directed. The Declaration was submitted to address this issue alone. See page 14 of Applicants' Response dated July 10, 2003. There should be no confusion, therefore, about why the Declaration was presented and no reason to believe that it addresses the issue of adequate description of compounds.

Rejection Based On Inadequate Disclosure of Compounds

The rejection to which the Examiner refers was first submitted in an Office Action dated October 25, 2001. The Examiner stated that compounds are critical to practice the claimed invention and, as such, the structures must be known. The fact that no specific compounds were described in the specification clearly was the sole basis for the rejection. In Applicants' Response dated April 25, 2002, Applicants asserted that it was the policy of the PTO to allow drug screening claims without a description of the compounds because the PTO realized that random compounds were routinely tested. Applicants cited a slide presentation to this effect given by Brian Stanton at a Biotechnology Partnership meeting. See pages 7, 8, and 10 of Applicants' April 25, 2002 Response. Applicants also submitted an expert

Declaration on April 24, 2002 by Dr. Youssef L. Bennani, Director of Medicinal Chemistry at Athersys, Inc., explaining scientifically why, for compound testing, the structure of the test compound was not critical (page 3 of the Declaration).

The rejection was maintained for reasons of record. In a subsequent interview with the Examiner and Brian Stanton, Mr. Stanton indicated that if indeed the claims were generic drug discovery claims then the compounds need not be described. The rejection was subsequently withdrawn. In the further Action of August 5, 2003, the Examiner indicated that the rejection was withdrawn on the basis of the Dhanoa Declaration. The Dhanoa Declaration clearly did not address compound description. Therefore, Applicants assumed this was an inadvertent erroneous statement.

Written Description Can Be Inherent

The Examiner seems to suggest that an artisan would not have known what the Applicants meant by the term "drug discovery." However, the term "drug discovery" was generally well-understood in the art, and an artisan would have known what steps the Applicants had in mind when they referred to "drug discovery" even though the specifics of these steps were not described in the application in the exact words used in the claims. As the CCPA stated, "the invention claimed does not have to be described in ipsis verbis to satisfy the description requirement of §112." *In re Lukach*, 58 C.C.P.A. 1233, 1235 (CCPA, 1971). "The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon 'reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter.'" *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772

F.2d 1570, 1575, 227 U.S.P.Q. (BNA) 177, 179 (Fed. Cir. 1985). This applies to the present case, according to the Dhanoa Declaration.

Subject Matter of Dhanoa Declaration

The Dhanoa Declaration plainly addresses the issue of whether the specification leads an artisan to the steps recited in claims. The Declaration states that steps recited in claims are inherent in the disclosure. Dr. Dhanoa has explained how the artisan would have known what specific steps were contemplated.

The Dhanoa Declaration plainly states that an artisan would have realized that, by disclosing "drug discovery," Applicants implicitly described the claimed drug discovery method. Having described the process of drug discovery, Dr. Dhanoa stated: "...the cited passages (referring to drug discovery), within the full context of the application, would have indicated to me that a compound could be tested against a RAGE cell with an activated gene of interest to determine if the compound affects the gene of interest or phenotype of interest." Dhanoa Declaration, page 9. The Examiner provides no evidence contradicting this statement.

Furthermore, the Bennani Declaration, presented on April 24, 2002 by Dr. Youssef L. Bennani, Director of Medicinal Chemistry at Athersys, Inc., states that, "[I]n my experience, the person of ordinary skill in the art (i.e., drug discovery) would immediately recognize the claimed method in the term "drug discovery" and would know how to use the RAGE-activated cells for drug discovery, including the well-known and fundamental steps used in

such research field." Bennani Declaration, page 5. Again, the Examiner provides no evidence contradicting this expert opinion.

Dhanoa Declaration Impermissibly Dismissed/Examiner Has Not Met Burden

First, the Declaration is not considered for what it does address. Therefore, it has not been properly considered on the relevant issue. Accordingly, the rejection is, at best, incomplete.

Next, the Declaration is also dismissed for impermissible reasons. There is no scientific or logical rebuttal of the evidence presented in the Declaration. The Examiner merely repeats the same unsubstantiated position as follows.

> How could the specification lead an artisan to the specific steps recited in the claim? In other words, how would an artisan know what specific steps were contemplated by the Applicants at the time of the invention. And the declaration cannot address this issue.

This fails to constitute scientific or logical reasons to rebut the evidence presented in the Declaration. Furthermore, the Declaration does address this issue. Accordingly, the Examiner has merely and impermissibly substituted his opinion for an expert's opinion which was based on sound scientific reasons about what the ordinary skilled artisan would have understood from the Applicants' specification.

No Precedent For Challenging the Mental Process of Declarant

The Examiner states that Dr. Dhanoa reached the wrong conclusion because of the *order* in which he *may* have reviewed the file history.

> Furthermore, from the declaration it is also unclear whether Dr. Dhanoa saw the claims and the rejection first before seeing the specification language because this would result in Dr. Dhanoa analyzing the specification keeping in mind the claim language.

The Examiner cites no case law or administrative regulations which specify how an expert is supposed to assess the facts, and, specifically, which would regulate whether or not an expert may see the disputed claims and the rejection before rendering his or her opinion. Applicants are unaware of any case law or administrative regulations where speculation about how an analysis was done adequately meets the burden for an Examiner to rebut an expert declarant. Even if Dr. Dhanoa's review was in the order suggested by the Examiner, Applicants are still unaware of any precedent showing that this type of review would be sufficient for an Examiner to meet the burden of rebutting an expert declarant. It must be presumed that an expert in the field can review the file history in any sequence they choose and still reach an objective conclusion based on sound scientific evidence or reasoning. The Examiner has not shown that Dr. Dhanoa failed to reach such an objective conclusion.

Dr. Dhanoa Discussed Patent Application 08/941,223

The Examiner focused on the fact that the Dhanoa Declaration lists 09/941,223 as a U.S. Patent Application, instead of 08/941,223. The Examiner states that "it is not clear which patent application did Dr. Dhanoa see."

In his Declaration, Dr. Dhanoa inadvertently mistyped the application number as 09/941,223 instead of 08/941,223. However, there is no any doubt as to which application Dr. Dhanoa saw. As the Examiner himself pointed out, there is no application number

09/941,223. The only application which discusses the RAGE technology and which was filed on September 26, 1997 is the application number 08/941,223. There simply is no other application to confuse it with.

Therefore, it is certain that Dr. Dhanoa discussed the Patent Application 08/941,223.

Summary Conclusion

Applicants have presented ample evidence that the specification disclosed the specific method claimed. The scientific evidence and reasoning in the Declaration has not been challenged with scientific or logical evidence. Therefore, Dr. Dhanoa's conclusion must be accepted. It is error to dismiss the Declarant's testimony without adequately articulating the reasons why the testimony fails to overcome the determination to reject the Applicants' application. *In re Alton*, 76 F.3d 1168 (Fed. Cir. 1996); *In re Oetiker*, 977 F.2d 1443 (Fed. Cir. 1992). With regard to the Dhanoa and Bennani Declarations, Applicants point out that they are offering factual evidence relating to drug discovery methods and the Declarants' understanding of the invention. The Federal Circuit cautioned that such factual evidence should not be dismissed lightly. *In re Alton*, at 1175.

The Declaration has not been properly considered for its pertinent teachings. Applicants respectfully submit that if the rejection is maintained then it is incumbent on the Examiner to reconsider the Dhanoa Declaration for its substantive teachings that are pertinent to this rejection. If the rejection is maintained in the face of the substantive teachings of the Declaration, sufficient evidence must be presented by the Examiner to rebut the expert conclusion. Otherwise, the rejection must be withdrawn.

Applicants submit that the totality of the record, consisting of the Applicants' disclosure, arguments, and two Declarations by experts in the field, points to the conclusion that the specification adequately discloses the claimed method. Reconsideration of the rejection and withdrawal is requested.

B. Rejection of Claims 69 and 70 under 35 U.S.C. §112, First Paragraph (Enablement)

On page 5 of the Office Action, claims 69 and 70 remain rejected under 35 U.S.C. §112, first paragraph, as "failing to comply with the enablement requirement for reasons of record set forth in the previous office action of 12/23/03." Applicants respectfully traverse the rejection.

The Examiner frames the issues as follows:

(i) the specification does not teach any method of drug discovery, either using cells or protein product purified from cells. The only references to a term "drug discovery" are on pages 7 and 11, however, these sections of the specification do not teach how to practice the claimed drug discovery methods.

(ii) It would not have been routine to determine the ability of one or more compounds to interact with the product of the activated gene since such would have depended on the characteristics/properties of the gene or gene product and the compound. This in turn would require characterization of the gene or gene product and a compound, which could interact with the gene product.

The Specification Teaches Drug Discovery Using RAGE-activated Cells

The first issue framed by the Examiner is essentially the same argument advanced in the above rejection. The Examiner claims that the specification does not teach any method of drug discovery and states that the only references to drug discovery are on pages 7 and 11 of the application. This is incorrect since there are other references in the application, as Applicants have previously pointed out.

In addition to pages 7 and 11, there are references to use the invention for drug discovery on pages 32, 35, and 69 of the application. In addition, the earliest priority application 08/941,223 also contains references to drug discovery on pages 5, 9, 12, 16, and 45. The Examiner also noted it on page 3 of the Office Action.

Applicants believe that they sufficiently addressed the point of the alleged non-teaching of drug discovery methods above. Two Declarations, present in the record (the Bennani Declaration and the Dhanoa Declaration), demonstrate that the person of ordinary skill in the art of drug discovery would have understood that the application adequately disclosed the claimed invention. The Examiner presented no evidence which would demonstrate that an artisan would not have been able to practice the claimed drug discovery methods. Therefore, the only evidence in the record is that the specification adequately teaches the use of RAGE-activated cells for drug discovery.

Since the person of ordinary skill would have understood that the specification disclosed the claimed invention then the only question is whether the person of ordinary skill

could have practiced each of the steps without undue burden of experimentation. The Examiner has already acknowledged that steps (b) – (d) are routine. Accordingly, the Examiner takes the position that step (e) was not routine. Applicants have already explained why step (e) would be routine and summarize briefly below.

It is Routine to Determine Whether a Test Compound Affects the Phenotype or Interacts with a Product of a Desired Activated Gene

The Examiner asserts that it is necessary to know the characteristics/properties of both a gene and a test compound to determine the ability of the test compound to interact with a product of the gene. Applicants have already explained in detail how compound testing in drug discovery is done with random compounds. See the Bennani Declaration, page 3, for example.

Applicants underscore that the claimed methods recite a "desired gene." Since the gene is desired, it is by definition known. Since the method can be used for different known genes, characteristics/properties of the genes would differ because different known genes have different characteristics/properties. Applicants stress that it is not required to know all characteristics and properties of a known gene to practice the claimed methods.

The claims recite "determining the ability of said one or more test compounds to interact with a product of said desired activated gene or to affect said desired phenotype." This step implies that artisans would use available assays for a particular desired gene or desired phenotype. There are many assays existing in the art for various genes and

phenotypes. If an artisan is interested in a particular gene, he would use an assay available for that gene to determine the effect of various test compounds on the gene. Likewise, if an artisan wants to determine whether a test compound affects a specific phenotype, the artisan simply determines whether a test compound affects the phenotype in some way using a suitable assay.

The Examiner states that it is relevant to know whether one or multiple genes affect the phenotype "since the method is for finding a drug for a certain gene." Applicants respectfully disagree. While in one embodiment of the invention the method can be used to find a drug for a certain gene, in other embodiments, the method can be used without knowing a gene or genes responsible for a specific phenotype. The claims do not recite a method for finding a compound for a certain gene. Claims are directed to "a method for drug discovery" which may include both finding compounds that affect specific genes and compounds that affect specific phenotypes without reference to any specific gene.

For example, suppose that a desired phenotype is resistance to a protease inhibitor. An artisan would introduce a vector into cells, culture the cells, and screen for cells having the resistance phenotype. Then, the artisan would expose the cells having the phenotype (resistance) to various test compounds to determine if any test compound has an effect on the phenotype (resistance). Because only an effect on the phenotype (resistance) is assayed, knowledge of the gene (or genes) that cause the phenotype (resistance) is not necessary. All the artisan is interested in is whether a test compound affects the phenotype (resistance).

Thus, the Examiner's assertion that "...the method is for screening of compounds that affect gene product of a gene and not for screening of compounds that affect drug resistance" is incorrect. One would, in fact, screen for compounds that affect drug resistance if that is the desired phenotype. The method recites determining the ability of a test compound to affect a desired phenotype. Therefore, the method encompasses screening compounds which affect the desired phenotype of drug resistance irrespective of the gene or genes that cause it.

There is No Need to Know the Structure of Test Compounds

The Bennani Declaration explained that in drug discovery, an artisan would test randomly selected compounds. The Examiner dismisses the Declaration as follows:

> Applicants arguments that an artisan could take any compound (as discussed in the declaration by Bennani) are not persuasive because an artisan would need to know the structure of the compound, structure of the gene product and requirements for the interaction of the compound to interact with a gene product to practice step (e). Applicants do not discuss where the specification discusses how to determine the ability of one or more compounds to interact with a product of an activated gene, which characteristics of a gene product or compound will be used in determining such.

The Examiner's statement does not provide sufficient evidence to rebut the statements of Dr. Bennani, which are based on his scientific experience. The Examiner simply reasserts his position without any scientific rebuttal evidence. Contrary to the Examiner's statement, Dr. Bennani has shown why an artisan would not need to know the structure of a test compound to practice step (e). As long as there is an assay to determine the effect of a test compound on a particular gene's expression or on a particular phenotype, the structure of the test compound is irrelevant. As Dr. Bennani explained, in drug discovery test compounds are typically taken "off the shelf" and are exposed to cells to assess their effect on a particular

gene or a phenotype. Assays are specifically designed to be able to measure the effect of any compound on a desired gene or a phenotype. Therefore, the structure of test compounds is irrelevant.

Schemes and Diagrams Were Provided to Assist the Examiner and Are Not Necessary to Understand the Claimed Invention.

The Examiner states that "while applicants provide elaborate schemes and explanations, none of these are present in the specification and therefore an artisan would not have had these descriptions for practicing the claimed invention."

Applicants provided schematic explanations showing how the invention works with a sole reason: to assist the Examiner to understand the invention. Applicants believed that these schemes and diagrams would save the Examiner's valuable time. The person of ordinary skill in the art would not have needed this assistance.

Accordingly, Applicants believe that they have addressed each of the grounds of the rejection and the rejection has been overcome. Reconsideration and withdrawal of the rejection is respectfully requested.

SUMMARY

In view of the remarks set forth above, it is respectfully submitted that this application is in condition for allowance.

The Commissioner is hereby authorized to charge any fee deficiency to Deposit Account No. 12-0080 referencing Attorney Docket No. ATX-007CP4DV12.

Respectfully submitted,

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APPENDIX A

PROPOSED CLAIMS PRESENTED IN AMENDMENT DATED JULY 10, 2003
U.S. SERIAL NO. 09/484,331

Claims 1-61 (canceled).

62. (currently amended) A method for drug discovery comprising:

(a) integrating a vector comprising a transcriptional regulatory sequence into the genome of one or more eukaryotic cells, wherein said vector integration activates expression of an endogenous gene, by means of said transcriptional regulatory sequence, in said one or more cells;

(b) culturing said one or more cells under conditions favoring expression of said activated gene, thereby producing a gene product of said activated gene;

(c) screening said one or more cells from step (b) for a cell in which a desired gene is activated or for a cell in which a desired phenotype is induced by said activated gene;

(d) treating said cell, in which said desired gene is activated or in which said desired phenotype is induced, with one or more test compounds; and

(e) determining the ability of said one or more test compounds to interact with a product of said desired activated gene.

63. (currently canceled) A method for drug discovery comprising:

(a) integrating a vector into the genome of one or more eukaryotic cells, wherein said vector integration activates expression of an endogenous gene in said one or more cells;

(b) culturing said one or more cells in reduced-serum cell culture medium under conditions favoring production of a protein encoded by said activated gene and secretion of said protein into the cell culture medium;

(c) screening said one or more cells for a cell in which a desired gene is activated and the protein encoded by said desired gene is secreted into the cell culture medium; and

(d) screening one or more test compounds for drug activity by determining the ability of said test compounds to interact with said secreted protein in said cell culture medium.

64. (currently canceled) The method of claim 63, further comprising concentrating said cell culture medium prior to said screening in (d).

65. (currently canceled) The method of claim 63, further comprising isolating said protein prior to said screening in (d).

66. (currently canceled) The method of claim 62 wherein said vector comprises a transcriptional regulatory sequence and wherein expression of said endogenous gene is activated by means of said transcriptional regulatory sequence.

67. (currently canceled) The method of claim 63 wherein said vector comprises a transcriptional regulatory sequence and wherein expression of said endogenous gene is activated by means of said transcriptional regulatory sequence.

68. (currently amended) The method of claim 62 wherein said vector integrates into the genome by non-homologous recombination.

69. (previously added) A method for drug discovery comprising:

(a) integrating a vector, comprising a promoter, into the genome of one or more eukaryotic cells, by non-homologous recombination, wherein said promoter activates expression of an endogenous gene in said one or more cells;

(b) culturing said one or more cells under conditions favoring expression of said activated gene, thereby producing a gene product of said activated gene;

(c) screening said one or more cells for a cell in which a desired gene is activated or for a cell in which a desired phenotype is induced by said activated gene;

(d) treating said cell, in which said desired gene is activated or in which said desired phenotype is induced, with one or more test compounds to be screened for drug activity; and

(e) determining the ability of said one or more test compounds to interact with a product of said desired activated gene or to affect said desired phenotype.

70. (currently added) The method of claim 62 or claim 69 wherein the gene product is protein, the protein is purified from the cell and the test compound is exposed to the purified protein.